HeRO® *solo*

&

HeRO® *duet*

Version 3.1

System Manual

MPSC

The Power To Predict

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Electronic Access to HeRO System Manuals

HeRO User Manuals are available in electronic form. To access the electronic copies of the documents, you will need a device connected to the Internet and have installed Adobe Acrobat Reader. There is a link to obtain Adobe Acrobat Reader on the HeRO website.

You can access the HeRO website by clicking "Help" from a HeRO screen, or by typing http://www.heroscore.com/Technical_Support.htm from a web browser. If you need help accessing the electronic copies of the documents or to request a printed copy at any time contact the appropriate representative on page 2 of this manual.

Single printed copies are available at no additional cost and will be delivered within seven days of receiving the request.

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Introduction

HeRO provides an automated, noninvasive method to detect transient decelerations and reduced baseline heart rate variability. **HeRO** continuously acquires, records, measures and analyzes variations in RR Intervals, and provides ongoing display of this information.

HeRO is used to:

- Continuously acquire heart rate data from an existing physiological monitor
- Identify and determine the length of time between individual heart beats (the R-R Interval)
- Calculate a set of measures from these R-R Intervals to characterize the heart rate pattern
- Compute an "index" based on the degree of decelerations and reduced baseline variability in these patterns,
- Calculate the **HeRO Score**, which expresses the index as a fold-increase risk of sepsis relative to the overall NICU population, and
- Provide this information to clinicians in a timely and intuitive fashion.

HeRO *solo* and ***HeRO duet*** are self-contained implementations of **HeRO** and are built upon the same technology platform. The monitors share a hardware platform, with the difference being in the number of patients monitored. Each processes ECG data from one (***solo***) or two (***duet***) patient monitors and shows **HeRO Scores** for the monitored bed(s).

In this document, **HeRO *solo*** or **HeRO *duet*** refer to the **HeRO Display** and, as applicable, the **HeRO Data Acquisition Device (AD2).**

Indications for Use

HeRO is intended to acquire, store, analyze, and report on ECG data collected from infants. **HeRO** is intended to be used by trained operators under the direct supervision of a licensed health care practitioner in a hospital neonatal or pediatric ICU environment.

HeRO is intended to be used for the analysis of the variability in RR Intervals (heart rate) and to report measurements of the variability of heart rate data (HRV). The HRV measurements reported by **HeRO** are specialized in nature, and intended to identify periods of transient decelerations and/or reduced baseline variability in the heart rate.

HeRO is intended to provide specialized HRV measurements and may detect arrhythmias, that when combined with other risk factors, can be used as an aid in assessing the risk of sepsis in infants. The use of **HeRO** monitoring improves survival in very low birth weight neonates.

HeRO *solo* and **HeRO *duet*** acquire data from a user-supplied ECG monitor.

Initial training and support are to be performed by Medical Predictive Science Corporation employees or contractors who have been certified by Medical Predictive Science Corporation as qualified to perform such duties. Assembly, relocation, and ongoing maintenance are the responsibility of the user.

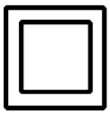
Contraindications

Patients with erratic, accelerated, or mechanically controlled irregular heart rhythms are not suitable for HRV evaluation. When shown, the ECG waveform displayed on the computer screen is not to be used for analysis of cardiac function.

Precautions

As is customary with good medical practice, the interpretation of any medical data should be made in conjunction with all other available medical history and diagnostic information about a patient. A low **HeRO Score** should never be used to deny or reduce treatment on a patient that is exhibiting clinical signs of sepsis.

HeRO *solo* and **HeRO *duet*** are not suitable for use in the presence of flammable anesthetic in mixture with air, oxygen, or nitrous oxide.



The **HeRO Data Acquisition Device (AD2)** is a Class II device and intended to be used only with the following supplied power adapter:

GlobTek, Inc. Model GTM21089-1305-T2 5.0V, 2.6A Medical Power Supply.

The **HeRO Display** is a Class I device and intended to be used only with the following power adapters:

SINPRO, Inc. Model MPU50-105 12.0V, 3.75A Medical Power Supply, or MPSC supplied equivalent.

Warning: To avoid the risk of electric shock, this equipment must only be connected to a supply mains with protective earth.

Warning: The SINPRO power supply must only be plugged into the **HeRO Display**, through the power port on the bottom. Attaching this power supply to the **HeRO Data Acquisition Device (AD2)** may cause damage to the **HeRO Data Acquisition Device (AD2)**.

Warning: This equipment is intended for use by healthcare professionals only.

Warning: The **HeRO Data Acquisition Device (AD2)** requires a minimum ECG waveform amplitude (at the ECG monitor Defib/Sync port) of +/- 1 volt (i.e. 2 volts peak to peak) for correct operation. Operation with lower amplitude input signals may cause inaccurate results.

Warning: **HeRO *solo*** and **HeRO *duet*** are classified as Medical Electronic Equipment. As such, they require special precautions regarding Electromagnetic Compatibility (EMC). Refer to the **HeRO Technical Information and Installation Guidelines** section for more information.

Warning: Other software applications should not be installed on the **HeRO Display**.

Environmental Requirements

The following environmental requirements apply to the hardware components of the **HeRO** system (i.e. the Server computer, dedicated Viewing Stations, and AD2-DAD devices with their associated cabling, if present).

Parameter	Operating Range	Storage/Transport Range
Temperature	0°C / 50°C	−30°C / 60°C
Relative Humidity	30% - 80% RH	10% - 95% RH
Altitude	0 m - 5000 m	0 m - 12000 m

Using this Manual

This manual is written for physicians, clinicians, nurses, care extenders and hospital IT personnel who are familiar with basic Windows software operation.

Clickable menu items or button names are designated by a box around the name, i.e. **Help**.

Labels of non-interactive graphs, or screen displays are indicated by bold type, i.e. **Patient View**.

The symbol is used in this manual and in the online help system to highlight warnings that could potentially affect patient care if not followed.

Overview

HeRO *solo* and **HeRO *duet*** are standalone monitoring systems that acquire heart rate data from an existing physiological monitor or monitors. **HeRO Scores** for the patient(s) being monitored are computed hourly and displayed on the **HeRO Display**.

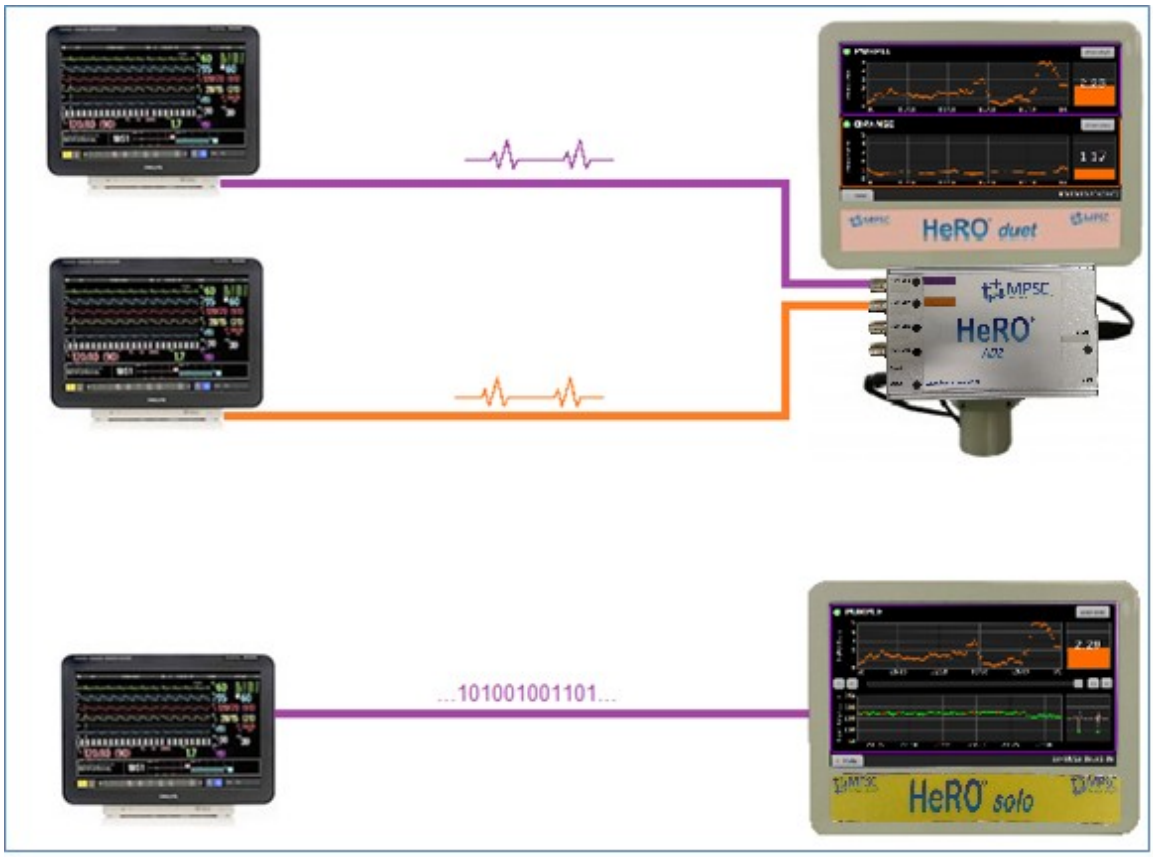


Figure 1: HeRO *solo* and *duet* Overview. Above, a **HeRO *duet*** configured to acquire the analog ECG waveform from the Defib/Sync jacks on two monitors using the optional **HeRO Data Acquisition Device (AD2)** . Below, a **HeRO *solo*** configured to acquire RS-232 heart rate data directly into the **HeRO Display**.

Data Acquisition

The **HeRO Data Acquisition Device (AD2)** is used to gather ECG waveform data from an existing physiological monitor and perform mathematical algorithms to determine patterns of HRV. The **HeRO Data Acquisition Device (AD2)** is a small, brick-sized device that is connected to an analog signal output on the physiological monitor and to the **HeRO Display**. Alternately, the **HeRO Display** can be connected directly to the RS-232 port on certain physiological monitors, and the **HeRO Data Acquisition Device (AD2)** is not needed. When connected via RS-232, **HeRO** will use the ECG-derived heart rate if available, or the SpO2-derived

pulse otherwise. Both the **HeRO Display** and the **HeRO Data Acquisition Device (AD2)** are approved for installation in the patient environment.

Using HeRO *solo* and HeRO *duet*

Setting Up

HeRO *solo* and **HeRO *duet*** are configured by MPSC prior to shipment. Instructions for assembly are included in the packing box and can be completed by hospital personnel. Relocation and ongoing maintenance are the responsibility of the user facility.

Below is an example of a **HeRO *duet*** with cables for two patients, one purple and one orange, that are connected to the **HeRO Data Acquisition Device (AD2)** as shown in Figure 2. (**HeRO *solo*** hardware appears identical, omitting the Channel 1 orange patient cable. RS-232 configurations, meanwhile, omit the **HeRO Data Acquisition Device (AD2)** entirely.)

Figure 2. **HeRO *duet*** cabling. The purple patient cable is inserted into the top port, and the orange cable in the second port. An Ethernet cable connects the **HeRO Data Acquisition Device (AD2)** to the HeRO display. **HeRO *solo*** cabling is identical except for the omission of the second, orange patient cable. RS-232 installations omit the **HeRO Data Acquisition Device (AD2)** entirely.

Powering down

Please turn off the **HeRO *solo*** or **HeRO *duet*** before unplugging any of the power cords connected to the unit. To do this press the circular power button ⏻ on the back of the **HeRO Display** and wait for the unit to shut down.

Viewing the HeRO Score

Each **HeRO** ***solo*** displays the **HeRO Score** and trend for one patient.

Each **HeRO** ***duet*** displays the **HeRO Score** and trend for up to two patients (as shown in in Figure 3).

The **HeRO Display** shows the most recently computed **HeRO Score** for each patient as a numeric value, and also shows a graph that trends the values over the last five days.

HeRO computes a new **HeRO Score** for each patient at the top of each hour (1:00, 2:00, etc). When a new patient is connected to the monitor, it may take up to 3 hours for the first score to be shown.

HeRO will stop generating scores for an individual patient if there is an insufficient amount of heart rate data or if there is not enough recent heart rate data to generate an accurate score. These gaps in the **HeRO Score** trend can occur if the patient leaves the bed, if the heart rate signal is otherwise interrupted for 30 minutes or more, or for patients with low heart rates due to cooling. When valid heart rate signal is restored, **HeRO** will resume generating scores as soon as enough new data is available. This may take up to an additional 3 hours.

***duet* View (only available on HeRO *duet*)**

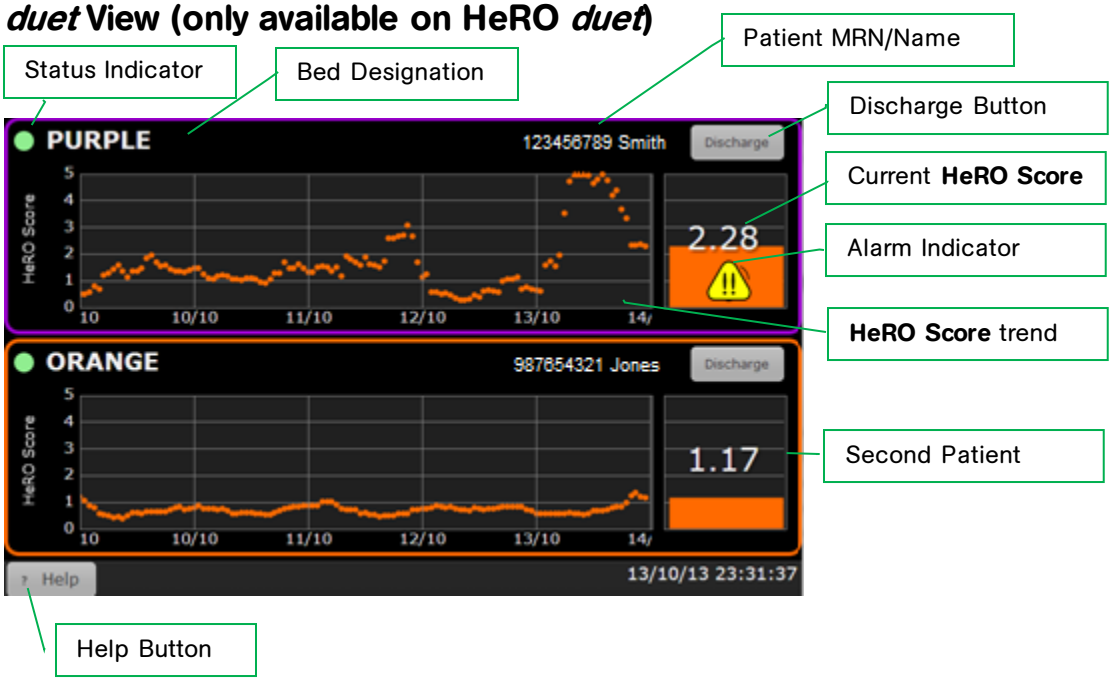


Figure 3. ***duet* View** Screen. **HeRO Scores** are shown for two beds labeled "Purple" and "Orange".

The ***duet* View** provides the most recent **HeRO Score** and 5-day trend for two patients. The elements composing each **Bed Icon** are:

- the bed designation (Purple or Orange for **HeRO Data Acquisition Device (AD2)** systems, the Bed Label of the monitor for RS-232 systems),
- The Name and MRN of the patient (RS-232 systems only)
- a five-day trend of the **HeRO Score**,
- a bar graph that shows the current **HeRO Score**,
- a numeric display of the current **HeRO Score**,
- an alarm symbol, when appropriate, and
- a status indicator that is green when the system is receiving heart rate data for the bed, and dark otherwise.

The alarm is shown when the **HeRO Score** is above the alarm threshold. A flashing alarm can be paused by tapping anywhere on the **Bed Icon**, or by choosing **Pause Alarm** from the pop-up menu. Refer to the section **Alarms** for more information.

Tapping on a **Bed Icon** will bring up the **Patient View**. Note that if an alarm is active, the first tap on the **Bed Icon** will pause the alarm, and the second tap will open the **Patient View**.

Tap the **Help** button to display the online help (this manual). When the help screen is displayed, the button label will change to **Back**. Tap the button again to return to the ***duet* View**.

Patient View (HeRO *solo* and HeRO *duet*)

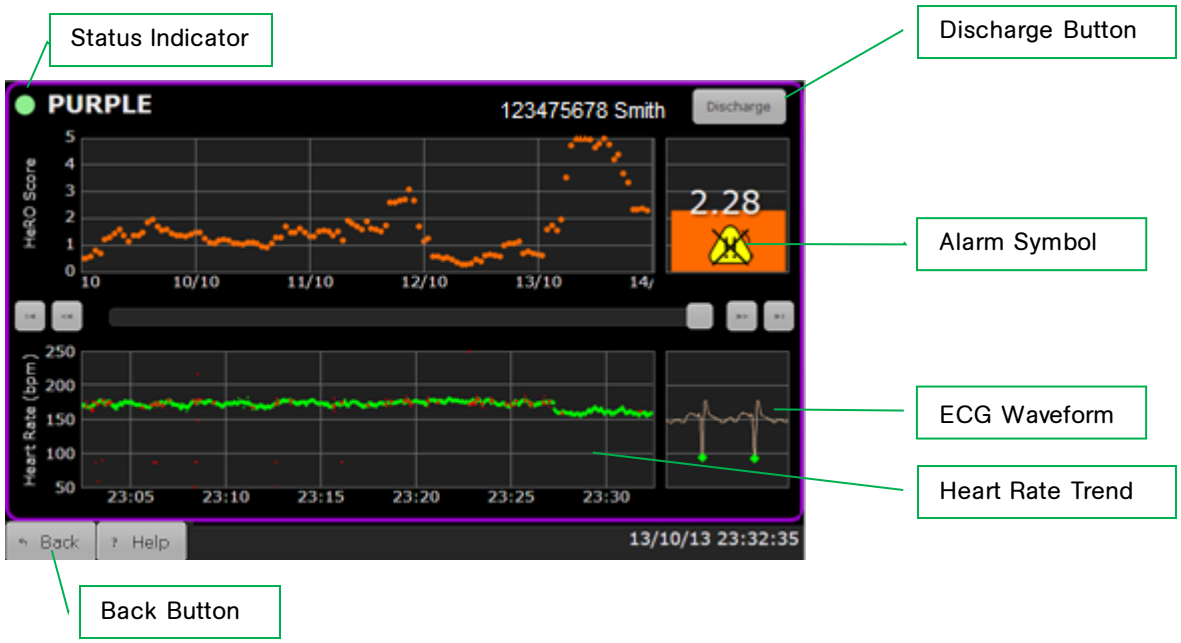


Figure 4. Patient View Screen

The **Patient View** covers a single bed, providing a more detailed look at the **HeRO** information. The **Patient View** contains the following elements:

- the bed identifier (Purple or Orange for **HeRO Data Acquisition Device (AD2)** systems, the Bed Label of the monitor for RS-232 systems),
- The Name and MRN of the patient (RS-232 systems only)
- a five-day trend of the **HeRO Score**,
- a bar graph that shows the **HeRO Score**,
- a numeric display of the **HeRO Score**,
- an alarm symbol, when appropriate,
- a 30-minute Heart Rate trend,
- a real-time ECG Waveform (when using the **HeRO Data Acquisition Device (AD2);** see warning below)
- a status indicator that is green when the system is receiving heart rate data for the bed.

The scroll bar and the four arrow buttons allow the user to navigate through several days worth of data. The 30-minute heart rate trend, the bar graph, and the numeric representation will display data from the currently selected time epoch. When historical data is being viewed, a yellow cursor in the **HeRO Score** trend indicates the location of the current time epoch.

The ECG waveform, when displayed by **HeRO,** should not be used as a diagnostic ECG. In addition, due to latency in the waveform display, this ECG trace should not be used as a trigger for defibrillation.

The alarm is shown when a patient's **HeRO Score** goes above the alarm threshold. A flashing alarm can be paused by tapping the alarm symbol or the surrounding bar graph area. Refer to the following section **Alarms**.

For **HeRO *duet***, tap the **Back** button to return to the ***duet* View**.

Discharge Button

Deletes all data for the currently displayed patient and clears the **HeRO Scores** from the ***duet* View** and the **Patient View**. Use this when connecting a new patient to the physiological monitor (this process will occur *automatically* when the serial RS-232 interface is used and HeRO detects a new Medical Record Number from the monitor).

You will be asked to confirm the **Discharge** operation before any changes are made. Data collection will resume immediately, but it may take up to 3 hours before the first **HeRO Score** is generated.

Activating HeRO *solo* and HeRO *duet*

HeRO *solo* is delivered configured to collect data from one physiological monitor. In order to begin generating **HeRO Scores**, the purple cable must be connected to the patient's physicological monitor.

HeRO *duet* is delivered configured to collect data from two physiological monitors. In order to begin generating **HeRO Scores**, the purple and orange cables must be connected to the patients' physiological monitors.

In both cases, please note the following:

- The typical time to generate the first **HeRO Score** for a new patient is 3 hours, and that **HeRO** utilizes up to the last 12 hours of heart rate data for each score generation. Thus, **HeRO** should remain dedicated to a patient bed for as long as possible.
- A **Discharge** operation must be completed any time the **HeRO *solo*** or ***duet*** is moved from one physiological monitor to another, or when a new patient is connected to the monitor.

Pausing an Alarm

HeRO *solo* and ***duet*** include a high score visual alarm to warn clinicians if a patient's score rises above an alarm threshold. When first activated, the alarm displays a flashing symbol. To pause the alarm (and stop the flashing), tap or click anywhere in the main area of the bed icon, away from the edges. Refer to the section **Alarms** for more information.

Continuous HeRO Monitoring

HeRO processes heart rate data and generates scores while the **HeRO Display** is running. However, monitoring is interrupted while the **HeRO Display** or the **HeRO Data Acquisition Device (AD2)** is powered off.

HeRO monitoring is active only when **HeRO Display** and **HeRO Data Acquisition Device (AD2)** are running.

Status and Error Messages

The top section of each bed in the ***duet* View** and the **Patient View** may display informational or error messages to indicate problems or status changes. These messages, and their meanings, are summarized below.

Message	Description
Comm Error	The **HeRO Display** is not able to communicate with the services that acquire data and generate **HeRO Scores**. This message may appear for up to 60 seconds when the patient monitor is first powered up. If the message does not disappear, there may be a hardware problem or a configuration error. Check power to the **HeRO Data Acquisition Device (AD2)** and reseat all communication cables to the **HeRO Display.**
HeRO is starting	The **HeRO** data processing services are starting. **HeRO** monitoring should begin within 5 minutes.
HeRO failed to start	**HeRO** data processing services could not be started. This may indicate a hardware problem or a configuration error.
Are you sure that you want to discharge bed (Purple/Orange)?	This message is displayed when the **Discharge** on the **Patient View** is clicked. No patient data has been changed at this point. You may choose to continue or cancel the operation.
Discharging bed (Purple/Orange)	A **Discharge** operation has been confirmed and is under way. The message will be cleared when the operation completes, and only indicates an error condition if the message does not disappear within 60 seconds.
Failed to discharge bed (Purple/Orange)	A **Discharge** operation has failed. Scores from the previous patient may still be displayed. Restart the **HeRO Display** unit and perform the operation again if necessary.
License is not valid	The software license is not valid.
License Expires	The software license has expired.

For more detailed information about these messages, and suggestions for diagnosing and resolving problems, refer to the **Troubleshooting** section of this manual. If the situation is not resolved by following the suggested steps, contact MPSC Technical Support .

Alarms

The **HeRO** System includes a visual high score alarm that is designed to draw attention to patients with elevated risk. The alarms activate when a patient's **HeRO Score** rises to, or beyond a threshold value.

The alarm state is indicated by one of the two Alarm Symbols shown below.

State	**Appearance**
Off	Symbol not shown
Active	 Symbol shown with exclamation points flashing
Paused	 Symbol shown with exclamation points solid

An active alarm may be paused by tapping the flashing symbol or the surrounding area. The alarm will now display the Paused symbol, which will remain visible until the alarm resets.

When the patient's score drops below the threshold, an Active or Paused alarm will reset to the Off state, and the alarm symbol will disappear. The alarm is automatically re-armed such that it will activate if the threshold value is exceeded in the future.

The alarm system in **HeRO** is implemented in software and does not require separate testing. If **HeRO** is operating, the alarm system is functional.

Interpreting Results

HeRO results provide a quantitative assessment of characteristic RR variability patterns, which may precede the clinical indications of developing illness. Clinical research has shown that reduced baseline variability and transient decelerations of heart rate (bradycardia) are related to fetal and neonatal distress[1]. The **HeRO Score** is reported as a fold increase in risk of sepsis relative to the general NICU population.

HeRO HRV data provides a new tool for clinical assessment so that standard diagnostic and therapeutic decisions are better founded. As is customary with good medical practice, the interpretation of any medical test should be made in conjunction with all other available medical history and diagnostic information about a patient.

Patients with high **HeRO Scores** (>2.0) are 6x more likely to develop sepsis in the next three days than patients with low **HeRO Scores** (<1.0). The **HeRO** system includes an alarm function to draw attention to these patients. Refer to the section **Alarms**.

A randomized controlled trial of 3,003 VLBW infants demonstrated that patients whose **HeRO Scores** were displayed to clinicians experienced 22% fewer deaths than patients whose **HeRO Scores** were not displayed to clinicians.

The computational methodology used to determine patient status is described in **Appendix A: Theory of Operation.**

Appendix C: Use of the HeRO Score in the Assessment of Infection provides numerous examples of **HeRO** trends around the time of clinically significant events.

Troubleshooting

Problem: **HeRO Main Window** is not visible

Description: **Main Window** is not shown on the **HeRO** Display.

Cause	Resolution
HeRO application screen does not appear, and unit displays the Windows desktop. Client application is not running	Manually start the **HeRO** application by double-tapping Windows desktop shortcut, or by selecting it in the Windows start menu.
HeRO Display will not start.	Restart **HeRO Display** by unplugging and replugging the monitor. Ensure that both the power cord for the **HeRO Display** and the **Data Acquisition Device (AD2)** are both plugged in to an energized power outlet.

Problem: *System Communication Error* message is displayed during normal use (not monitor start up)

Description: The **HeRO** window application is not able to communicate with the services that acquire data and generate **HeRO Scores**.

Cause	Resolution
HeRO is starting up	Wait for **HeRO Display** to initialize (up to 5 minutes).
Configuration error	Contact MPSC Technical Support.

Problem: *HeRO Failed to Start* message is displayed

Description: The **HeRO** data processing services did not start.

Cause	Resolution
Internal PC error	Reboot **HeRO Display** by unplugging and replugging the power cable.
Configuration error	Contact MPSC Technical Support.

Problem: *License is not valid* message is displayed

Description: The software license has an invalid signature or is otherwise corrupt.

Cause	Resolution
License file has been tampered with or was otherwise damaged.	Contact MPSC Technical Support

Problem: *License Expired* message is displayed

Description: The software license has expired.

Cause	Resolution
Expired license	Contact MPSC Sales or Technical Support

HeRO Technical Information and Installation Guidelines

The **HeRO Display** and **Data Acquistion Device (AD2)** are parts of the **HeRO *solo*** and ***duet***. The following information is provided for reference. For assistance with installation or reconfiguration, contact Technical Support.

Site Location

HeRO *solo* and **HeRO *duet*** are installed in the NICU. **HeRO** is approved for use within the "patient vicinity" that extends within 1.5 meters of the patient. The **HeRO Data Acquisition Device (AD2)** is an optional part of **HeRO**. Individual cables are run from the physiological monitors to the **HeRO *solo*** or ***duet***.

The **HeRO Data Acquisition Device (AD2)** is not approved for installation in close proximity to, or stacked with, other equipment that is sensitive to Radio Frequency (RF) or Electromagnetic Interference (EMI) emissions, or that generates significant RF or EMI emissions.

Cabling

HeRO requires the following connections and cable types:

Connection	Cable Type	Maximum Length	Notes
ECG signal input (from Defib/Sync or RS-232 jack on physiological monitor)	Proprietary	5 meters	• The cable end at the Defib/Sync or RS-232 jack is a manufacturer specific connector. • **HeRO** is intended to connect to one (***solo***) and up to 2 (***duet***) ECG monitors.
Data Acquisition Device (AD2) to **HeRO Display**	CAT5	0.5 meters	
Data Acquisition Device (AD2) Power	2 wire power cord (provided)	6 meters	The Data Acqusition Device (AD2) uses an external medical grade power supply rated for 110-240VAC input voltage. It is not approved for use with any other power supply. The Data Acquisition Device (AD2) is a CISPR11 Class A device and is not approved for use in buildings used for domestic purposes, or in other locations that directly connect

Connection	Cable Type	Maximum Length	Notes
			to the public low voltage power supply network that supplies buildings used for domestic purposes.
HeRO Display	3 wire power cord (provided)	6 meters	The **HeRO Display** uses an external medical grade power supply rated for 110-240VAC input voltage. It is not approved for use with any other power supply.

Connections using unapproved cable types or lengths may result in increased RF or EMI emissions or decreased immunity to these types of emissions.

Cleaning

The hardware components of **HeRO** ***solo*** or ***duet*** may be cleaned as needed per the instructions below.

HeRO Display, Data Acquisition Device (AD2), and cables

- Disconnect this equipment from any AC outlet before cleaning. The equipment can be wiped or dusted with a damp cloth. Do not use liquid or spray detergents for cleaning.

HeRO roll stand, desk stand, and wall mount

- The mounting assembly may be cleaned with most mild, non-abrasive solutions commonly used in the hospital environment (e.g. diluted bleach, ammonia, or alcohol solutions).
- The surface finish will be permanently damaged by strong chemicals and solvents such as acetone and trichloroethylene. Do not use steel wool or other abrasive material to clean the mounting assembly. Damage caused by the use of unapproved substances or processes will not be covered by warranty. We recommended that you test any cleaning solution on a small area of the mounting assembly that is not visible to verify compatibility.
- Never submerge the roll stand or allow liquids to enter the mounting assemblies. Wipe any cleaning agents off the mounting assembly immediately using a water-dampened cloth. Dry all mounting assemblies thoroughly after cleaning.

Description of Markings

The following markings are used on the **Data Acquisition Device (AD2)** labeling:

Marking	Description
	Manufacturer
	Class II equipment
	Consult Operating Instructions before use
	Medical Safety Certification
	Certification of conformity to European Community directives
	Do not dispose of equipment in trash. Return to manufacturer to be repaired or recycled.
	Contact information for European Community Representative.

The following markings are used on the **HeRO Display** labeling:

Marking	Description
	Manufacturer
	Medical Safety Certification
	Certification of conformity to European Community directives
	Do not dispose of equipment in trash. Return to manufacturer to be repaired or recycled.
	FCC-Approved Equipment Authorization.

Modifications

HeRO ***solo*** and ***duet*** are not user serviceable and must not be modified in any way. Defective units must be returned to MPSC for replacement.

HeRO is designed for continuous operation—the user should not turn off the device, or take any other steps, in order to reduce environmental impact.

Environmental Impact

HeRO ***solo*** and ***duet*** are designed to minimize impact on the environment. Due to the continuous nature of **HeRO** monitoring, it is not recommended that the system or its components be powered down at any point to conserve electricity. Follow the instructions on disposal above when removing **HeRO** from service.

Electrical Isolation

The **HeRO Data Acquisition Device (AD2)** is electrically isolated via the provided medical grade power supply, specified below. It is not approved for use with any other type of power supply.

- GlobTek, Inc. Model GTM21089-1305-T2 5.0V, 2.6A Medical Power Supply

The **HeRO Display** is electrically isolated via the provided medical grade power supply, specified below. It is not approved for use with any other type of power supply.

- SINPRO, Inc. Model MPU50-105 12.0V, 3.75A Medical Power Supply.

Electromagnetic Compatibility

Guidance and manufacturer's declaration – electromagnetic emissions		
The HeRO System is intended for use in the electromagnetic environment specified below. The customer or the user of the HeRO System should assure that it is used in such an environment.		
Emissions test	**Compliance**	**Electromagnetic environment – guidance**
RF emissions CISPR 11	Group 1	The HeRO system uses RF energy only for its internal function. Therefore, its RF emissions are very low and are not likely to cause any interference in nearby electronic equipment.
CISPR 11	Class A	The HeRO system is suitable for use in all establishments other than domestic and
Harmonic emissions	Class A/D	

IEC 61000-3-2		those directly connected to the public low - voltage pow er supply network that supplies buildings used for domestic purposes.
Voltage fluctuations/ flicker emissions IEC 61000-3-3	PASS	

Guidance and manufacturer's declaration – electromagnetic immunity

The HeRO system is intended for use in the electromagnetic environment specified below . The customer or the user of the HeRO system should assure that it is used in such an environment.

IMMUNITY test	IEC 60601 test level	Compliance level	Electromagnetic environment – Guidance
Electrostatic discharge (ESD) IEC 61000-4-2	± 6 kV contact ± 8 kV air	± 6 kV contact ± 8 kV air	Floors should be w ood, concrete or ceramic tile. If floors are covered with synthetic material, the relative humidity should be at least 30%.
Electrical fast transient/burst IEC 61000-4-4	± 2 kV for pow er supply lines ± 1 kV for input/output Lines	± 2 kV for pow er supply lines ± 1 kV for input/output Lines	Mains pow er quality should be that of a typical commercial or hospital environment.
Surge IEC 61000-4-5	± 1 kV line(s) to line(s) ± 2 kV line(s) to earth	± 1 kV line(s) to line(s) ± 2 kV line(s) to earth	Mains pow er quality should be that of a typical commercial or hospital environment.
Voltage dips, short interruptions and voltage variations on pow er supply input lines IEC 61000-4-11	<5 % U_T (>95 % dip in U_T) for 0,5 cycle 40 % U_T (60 % dip in U_T) for 5 cycles 70 % U_T (30 % dip in U_T) for 25 cycles <5 % U_T (>95 % dip in U_T) for 5 s	<5 % U_T (>95 % dip in U_T) for 0,5 cycle 40 % U_T (60 % dip in U_T) for 5 cycles 70 % U_T (30 % dip in U_T) for 25 cycles <5 % U_T (>95 % dip in U_T) for 5 s	Mains pow er quality should be that of a typical commercial or hospital environment. typical commercial or hospital environment. If the user of the HeRO System requires continued operation during pow er mains interruptions, it is recommended that the HeRO system be pow ered from an uninterruptible pow er supply or a battery.
Pow er frequency (50/60 Hz) magnetic field IEC 61000-4-8	3 A/m	3 A/m	Pow er frequency magnetic fields should be at levels characteristic of a typical location in a typical commercial or hospital environment.
NOTE U_T is the a.c. mains voltage prior to application of the test level.			

Guidance and manufacturer's declaration – electromagnetic immunity

The HeRO system is intended for use in the electromagnetic environment specified below. The customer or the user of the HeRO system should assure that it is used in such an environment.

IMMUNITY test	IEC 60601 test level	Compliance level	Electromagnetic environment – guidance
Conducted RF IEC 61000-4-6	3 Vrms 150 kHz to 80 MHz	3 V	Portable and mobile RF communications equipment should be used no closer to any part of the HeRO system, including cables, than the recommended separation distance calculated from the equation applicable to the frequency of the transmitter. **Recommended separation distance** $d = 1.2\sqrt{P}$ $d = 1.2\sqrt{P}$ 80 MHz to 800MHz $d = 2.3\sqrt{P}$ 800 MHz to 2.5GHz where *P* is the maximum output power rating of the transmitter in watts (W) according to the transmitter manufacturer and *d* is the recommended separation distance in metres (m). Field strengths from fixed RF transmitters, as determined by an electromagnetic site survey,[a] should be less than the compliance level in each frequency range.[b] Interference may occur in the vicinity of equipment marked with the following symbol:
Radiated RF IEC 61000-4-3	3 V/m 80 MHz to 2,5 GHz	3 V/m	

NOTE 1 At 80 MHz and 800 MHz, the higher frequency range applies.

NOTE 2 These guidelines may not apply in all situations. Electromagnetic propagation is affected by absorption and reflection from structures, objects and people.

[a] Field strengths from fixed transmitters, such as base stations for radio (cellular/cordless) telephones and land mobile radios, amateur radio, AM and FM radio broadcast and TV broadcast cannot be predicted theoretically with accuracy. To assess the electromagnetic environment due to fixed RF transmitters, an electromagnetic site survey should be considered. If the measured field strength in the location in which the HeRO system is used exceeds the applicable RF compliance level above, the HeRO system should be observed to verify normal operation. If abnormal performance is observed, additional measures may be necessary, such as re-orienting or relocating the HeRO system.

[b] Over the frequency range 150 kHz to 80 MHz, field strengths should be less than 3 V/m.

Recommended separation distances between portable and mobile RF communications equipment and the HeRO system

The HeRO system is intended for use in an electromagnetic environment in which radiated RF disturbances are controlled. The customer or the user of the HeRO system can help prevent electromagnetic interference by maintaining a minimum distance between portable and mobile RF communications equipment (transmitters) and the HeRO system as recommended below, according to the maximum output power of the communications equipment.

Rated maximum output power of transmitter W	**Separation distance according to frequency of transmitter** m		
	150 kHz to 80 MHz $d = 1.2\sqrt{P}$	**80 MHz to 800 MHz** $d = 1.2\sqrt{P}$	**800 MHz to 2,5 GHz** $d = 2.3\sqrt{P}$
0.01	0.12	0.12	0.23
0.1	0.38	0.38	0.73
1	1.2	1.2	2.3
10	3.8	3.8	7.3
100	12	12	23

For transmitters rated at a maximum output power not listed above, the recommended separation distance *d* in metres (m) can be estimated using the equation applicable to the frequency of the transmitter, where *P* is the maximum output power rating of the transmitter in watts (W) according to the transmitter manufacturer.

NOTE 1 At 80 MHz and 800 MHz, the separation distance for the higher frequency range applies.

NOTE 2 These guidelines may not apply in all situations. Electromagnetic propagation is affected by absorption and reflection from structures, objects and people.

Appendix A: Theory of Operation

HeRO uses sophisticated mathematical modeling techniques to analyze heart rate data for characteristic patterns of variability. In order to accomplish this, raw data must be screened and converted into a statistically useful form. Then, significant relationships must be calculated to determine the relative degree of transient decelerations and reduced baseline variability present in the heart rate data.

Algorithms for Calculating RRI Parameters

QRS Detection (where applicable)

The QRS detector of the **HeRO** system has been tuned for "quality", not "quantity". As such, observers may find that many seemingly valid QRS complexes are not identified by the system. This is consistent with the intended use of the device, which is to identify periods of transient decelerations and reduced baseline variability in the heart rate. As such, it is not as important that every single RR Interval be identified as it is that identified intervals be valid.

After the QRS detection algorithm identifies candidate QRS complexes, the corresponding intervals are checked for validity. Intervals that are outside of a range of +/- 20% of the mean of the last fifteen intervals are discarded. Also discarded are intervals whose difference from the previous interval is not within five standard deviations of the mean of the previous 512 differences. These rules are justified by the presence on all ECG waveforms of certain artifactual signals caused by myoelectrical noise, clinician interference, or other spurious inputs. When the signal-to-noise ratio of the true electrocardiograph drops below a certain level (caused by poor lead placement, inadequate electrode contact, etc), these spurious inputs can be mistakenly recognized as a QRS complex. The criteria for RR interval validation discussed above ensure that the subsequent HRV analyses are only performed on valid interval data.

While the rules above will inevitably lead to the rejection of some valid QRS complexes, and therefore to a bias toward reporting lower variability than actually exists, the system is still able to perform its intended function of identifying *reduced* variability and transient decelerations.

The operator can gain insight into the operations of the QRS detection algorithm and validation rules by observing the trends on the **Patient View** screen. On the ECG graph, QRS complexes marked with a green triangle indicate the termination of a valid RR Interval. Those with red marks indicate an invalid interval. Those with no marks indicate QRS complexes that were not identified by the system, and

usually occur during or immediately after a spurious ECG signal. The **Heart Rate** trend plots this information against time. Points plotted in green represent valid RR intervals, points in red represent invalid RR intervals, while epochs of time in which QRS complexes were not identified are represented by "gaps" in the **Heart Rate** trend. Note that subsequent data processing is not performed on data collected during time epochs in which the "gaps" occur, nor data marked as invalid.

Data Packaging

Sets of 4096 consecutive RR intervals are recorded, and the start and stop times noted. Each set represents 20 minutes (at a heart rate of 200 beats/min) to 41 minutes (at a heart rate of 100 beats/min). Sets with artifactual intervals are defined as:

- Lasting more than 45 minutes (heart rate less than 100 beats per minute)
- 5 consecutive minutes without detecting a heartbeat with valid RR interval values (at which point the RR interval is reset).

The data from these sets are not included in the analysis.

Data Conditioning Prior to Calculation of HRV

The mean RR interval is calculated on the raw data. The RR intervals are filtered by subtracting a (2M+1) point moving average window

$$RR(n) = \frac{1}{2M+1} \sum_{j=-M}^{M} RR(n-j)$$

where n is the index of the RR interval (1 to 4096) and M=100. The standard deviation of the filtered RR intervals is calculated. Then each RR interval is divided by the standard deviation. The result is a set of high-pass filtered, normalized RR intervals with mean ≈ 0 and standard deviation ≈ 1.

Mathematical Analysis

Histogram Based Parameters

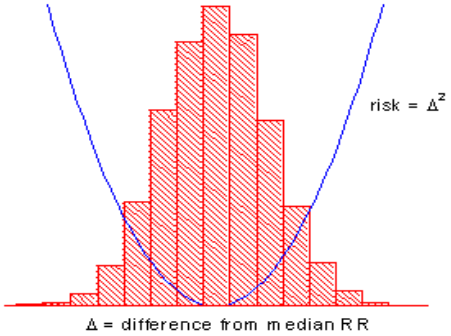
From each set of 4096 High-Pass filtered, normalized RR intervals, the 10th, 25th, 50th, 75th, and 90th percentiles and the first, second, third, and fourth moments are calculated.

Sample Asymmetry Analysis

One characteristic of transient decelerations is a marked asymmetry of the distribution of RR intervals accompanied by an occurrence of large deviations, especially to the right of the distribution median. This phenomenon is quantified

through Sample Asymmetry analysis. The first step is to construct a quadratic function that will be used for weighting the deviation of each RR interval from a median, computed on a data block containing 4096 beats (approximately 25 minutes of data). The Figure presents a function $r(x_i)=(x_i-m)^2$, where x_i is the magnitude of an RR interval # i and m is the median of the data. The two branches of this parabola quantify deviations towards increase (right half) and decrease (left half) of an RR interval with respect to the median. Given a series of (4,096) RR intervals $x_1, x_2, \ldots x_{4096}$, we compute $r_1(x_i)=r(x_i)$ if $x_i<m$, 0 otherwise; and $r_2(x_i)=r(x_i)$ if $x_i>m$, 0 otherwise for each RR reading x_i. Finally the R_1 (left asymmetry) and R_2 (right asymmetry) are computed as:

$$R_1 = \frac{1}{4096}\sum_{i=1}^{4096} r_1(x_i) \quad \text{and} \quad R_2 = \frac{1}{4096}\sum_{i=1}^{4096} r_2(x_i) \quad \text{respectively.}$$

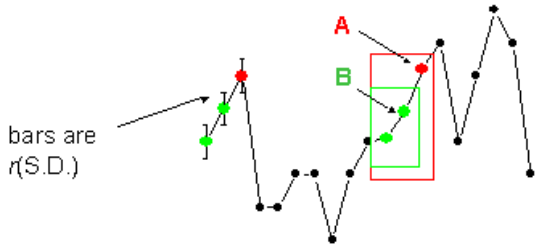


In other words, R1 and R2 are non-negative quantities that increase when the number and/or the magnitude of large deviations from the median increases. Intuitively, a distribution of RR intervals that is skewed to the right will result in R2 > R1.

Figure A1. Sample Asymmetry

Sample Entropy

Sample Entropy is a measure of regularity in time series that is suitable to HRV analysis[2]. Sample Entropy (m,r,N) is the negative natural log of the conditional probability that two sequences similar within a tolerance r for m points remain similar at the next point, where N is the total number of points and self-matches are not included. A low value of SampEn is interpreted as showing increased regularity or order in the data. SampEn is very similar to approximate entropy (ApEn) but has reduced bias, especially for short data sets. Sample entropy (SampEn) is calculated with m=3, r=0.2 using filtered, normalized data[3].



A = number of matches of length *m+1*
B = number of matches of length *m*

ApEn ≈ -ln (1+A)/(1+B)
SampEn = -ln A/B

For regular, repeating data, A/B nears 1 and entropy nears 0.

Figure A2. Sample Entropy

Mathematical Modeling

Logistic Regression

Since no single measure will reliably detect all of the abnormal records, multivariable predictive mathematical models are employed. One such model is a **logistic regression**.

The mathematical model uses variables for HRV measures including standard deviation, sample entropy, and asymmetry function analysis.

These variables are inserted into a logistic equation of the form:

$p = e^A / (1 + e^A)$

where

$A = \beta_0 + \beta_1 \bullet V_1 + \beta_2 \bullet V_2 + \ldots \beta n \bullet Vn$

and where $V_{1\ldots n}$ represent various measures of heart rate variability.

Fold Increase Score

The model output score is scaled by a constant to determine the Fold Increase Score. Computing this score is analogous to dividing a particular Logistic Regression score by the average Logistic Regression score seen in the overall NICU population. Thus, any score less than 1.0 is below average, while any score

above 1.0 is above average. The Fold Increase Score is graphed on a scale from 0.0 to 5.0.

HeRO Score

The **HeRO Score** is generated by taking the maximum of two Fold Increase scores, each of which is ultimately derived from a Logistic Regression equation with unique coefficients. Each of the sets of coefficients has been developed to address a specific heart rate pattern. Combining the outputs of different sets of coefficients yields a more sensitive result then a single set of coefficients can.

Please see the section *Interpreting Results* for a discussion of the relevance of the **HeRO Score**.

References:

[1]Griffin MP, Scollan DF, Moorman JR. The dynamic range of neonatal heart rate variability. *J. Cardiovascular Electrophysiology*. 1994; 5:112-124.

[2,3] Richman JS, Moorman JR. Physiological time-series analysis using approximate entropy and sample entropy. *American Journal of Physiology.* 2000;278:H2039-2049.

Appendix B: Glossary

ANOVA: Analysis Of Variance

Area under Receiver Operating Characteristics: a plot of sensitivity vs. specificity at a variety of thresholds. A totally random test produces an ROC area of 0.5, while a perfect test produces an ROC area of 1.0

Artifact or artefact: Spurious signal not consistent with the expected results. May be produced by a defective machine, electrical interference, patient movement or loose electrodes.

Bradycardia: slow heart beat

Cubic spline: a commonly used interpolation technique

Cumulative Distribution Function (CDF): the cumulative sum of the histogram of a set of data

Demographics: Statistical characteristics of the population (in this case , significant demographics include birth weight, gestational age and post-conceptional age)

ECG (or EKG)= electrocardiogram: Record of the electrical activity of the heart, showing waves called P, Q, R, S, and T waves. The Q, R, S and T waves are related to contraction of the ventricles

Fiduciary point: the single point representing the R-wave in a QRS complex

Gestational age: Prenatal age of fetus from conception to birth

High-pass filtering: a signal processing technique that removes low-frequency and DC components of a signal

Histogram: graph of frequency distribution by means of rectangles whose widths represent class (R-R) intervals and whose areas are proportional to the corresponding frequencies

HR: Heart Rate

HRV: Heart Rate Variability

Kurtosis: The peakedness or flatness of the graph of a frequency distribution (especially with respect to the concentration of values near the mean as compared with the normal distribution)

Logistic regression: a regression model that fits binary outputs to the curve represented by $e^a/(1+e^a)$

Model Output: Results of mathematical equation computed hourly; based on demographic data and/or RRI parameters collected in the preceding 12 hours (ex. Demographic Risk Model, HRV Score)

Moment: the expected value of a positive integral power of a random variable

Moving average window: A filter that averages a signal over a "window" of time

Normalization: Process by which a statistical moment is altered by subtracting the mean and dividing by the standard deviation, so that the Mean = 0 and the SD = 1.

P50: 50th percentile data point

Post-conceptional age: Current age of neonate, from conception to present

Reduced Baseline Variability: epochs of heart rate data in which the trend has "gone flat" or has less variability in the baseline heart rate. This is invariably linked to a decrease in the second moment (standard deviation).

ROC: Receiver Operating Characteristic

R-R Interval or RRI: Interval between heartbeats

RRI Parameter: A statistic computed on an RRI set of 4096 interval (ex. "M1" = mean of RRI

RRI Set: 4096 consecutive heartbeats (R-R intervals)

SD: Standard Deviation

SEM: Standard Error of the Mean

Signal processing: The process of breaking down an electrical signal into components that can be analyzed through a variety of algorithms

Skewness: Lack of symmetry in a frequency distribution. A symmetrical histogram has a skewness of 0, while a histogram with a tail of values larger than the median has a positive skewness.

Transient Deceleration: epochs of heart rate data in which the trend indicates a deceleration of the heart rate, for a period of roughly 30-100 heart beats (transient period), followed by an acceleration. These patterns are reflected by a decrease in Sample Entropy.

Appendix C: Use of HeRO Score in the Assessment of Infection

HeRO Clinical Instructions

The **HeRO Score** is to be used as another piece of adjunctive information in the assessment of sepsis.

The **HeRO Score** represents the fold-increase in risk that a particular patient will develop sepsis in the next 24 hours. For each patient monitored, the **HeRO Score** is generated each hour, based on the last 12 hours of heart rate data. Abnormal Heart Rate Characteristics (transient decelerations and reduced baseline variability) are detected and quantified by the **HeRO** algorithms to render the **HeRO Score**. The **HeRO Score** is considered:

Low if it is less than 1.0,
Intermediate if it is between 1.0 and 2.0,
High if it is above 2.0.

The **HeRO Score** is to be used alongside existing clinical observations such as increase in apneas and bradycardias, increase in oxygen or ventilation, feeding intolerance, hypotonia, lethargy, temperature instability, hypotension, grunting, vomiting, jaundice, shock, petechiae, purpura, or abdominal distention.

HeRO Score

Clinical Score

	Not measured		Low	Inter-mediate	High
Not measured	**1.0**		**<1**	**1-2**	**>2**
0	**0.7**		**0.5**	**1**	**2.5**
1	**2**		**1**	**2**	**4**
≥2	**3**		**3**	**3**	**4**

Figure C1. Sepsis Risk Scorecard. From Griffin, 2007, Heart Rate Characteristics and Clinical Signs in Neonatal Sepsis.

An elevated **HeRO Score** is not a diagnosis of sepsis; it is an indication that sepsis is more likely. While an elevated **HeRO Score** should arouse suspicion of sepsis, diagnosis must be confirmed with other clinical signs, laboratory work, and/or culture results.
Conversely, a low **HeRO Score** does not rule out sepsis; it indicates that sepsis is less likely. A patient that has a low **HeRO Score**, yet is exhibiting signs and symptoms of sepsis, should be evaluated without regard to the low **HeRO Score**. A low **HeRO Score** should not be used to withhold treatment.

Figure C1 shows a table for bedside use in estimating the risk of impending sepsis in the NICU using a clinical score and **HeRO** monitoring. The clinical score assesses points for the following conditions used in diagnosing sepsis: apnea, increased ventilatory support, temperature instability, lethargy or hypotonia, feeding intolerance, I:T ratio, WBC, and hyperglycemia. When neither the clinical score nor the **HeRO Score** is measured, the fold-increase in risk of illness is 1.0. The clinical score alone differentiates infants across a spectrum of risk, as does the **HeRO Score**. Knowledge of both allows greater refinement in the estimation of risk. For example, an infant with a clinical score of 0 generally has lower risk of illness, but the concurrent finding of a high-risk **HeRO Score** identifies a subset with 2.5-fold increase in risk. For infants with 2 points or more, that is, with clinical findings of illness, knowledge of the **HeRO Score** adds little and even a low-risk **HeRO Score** does not cancel out the clinical presentation. This is in keeping with the idea that the **HeRO Score** is adjunctive to clinical information, and is not a standalone substitute for medical personnel.

Other than sepsis, there are many reasons for an elevated **HeRO Score**. It is believed that an elevated level of circulating cytokines early in sepsis causes the SA node of the heart to respond abnormally to the parasympathetic and sympathetic branches of the autonomic nervous system. Hence, any condition that is believed to result in cytokine release is also likely to cause elevated **HeRO Scores**. These conditions include urinary tract infection, necrotizing enterocolitis, intraventricular hemorrhage, and respiratory distress, among others. It is also well known that anesthetics and vasodilators affect the autonomic nervous systems. Hence, patients returning from surgery or after a routine eye exam will have elevated **HeRO Scores**.

The **HeRO Score** can also be driven artificially low. Steroids are well known to suppress immune system activity, and thus cytokines. Patients on steroids have been observed to be in a state of super-variability in heart rate, thus driving their **HeRO Scores** down.

In most cases of sepsis, the **HeRO Score** correlates with the clinical symptoms: e.g. apneas and bradycardias are increased, the patient is feeding intolerant, the temperature is unstable, and the **HeRO Score** is rising. In very rare cases, even in

the presence of these other clinical abnormalities, the **HeRO Score** will remain low. However, the power of **HeRO** lies in the fact that in most cases of sepsis, the **HeRO Score** is an early manifestation of sepsis. In such a case, where the **HeRO Score** is high but the patient is clinically normal, the clinician is instructed to obtain lab work and treat based on the results. If the lab work returns normal, the clinician should continue to observe the patient. However, if the lab work is abnormal, the clinician should perform a sepsis work-up and initiate broad-spectrum antibiotic therapy. The culture results should be used to guide or discontinue future therapy.

Interpretation Examples

The following screenshots from the **HeRO** System represent one patient's stay in the NICU while monitored by the **HeRO** System (note that the **HeRO Scores** were generated but not displayed to clinicians). While the number of events experienced by this patient is unusual, the course of stay offers a remarkably broad set of clinical scenarios for interpretation.

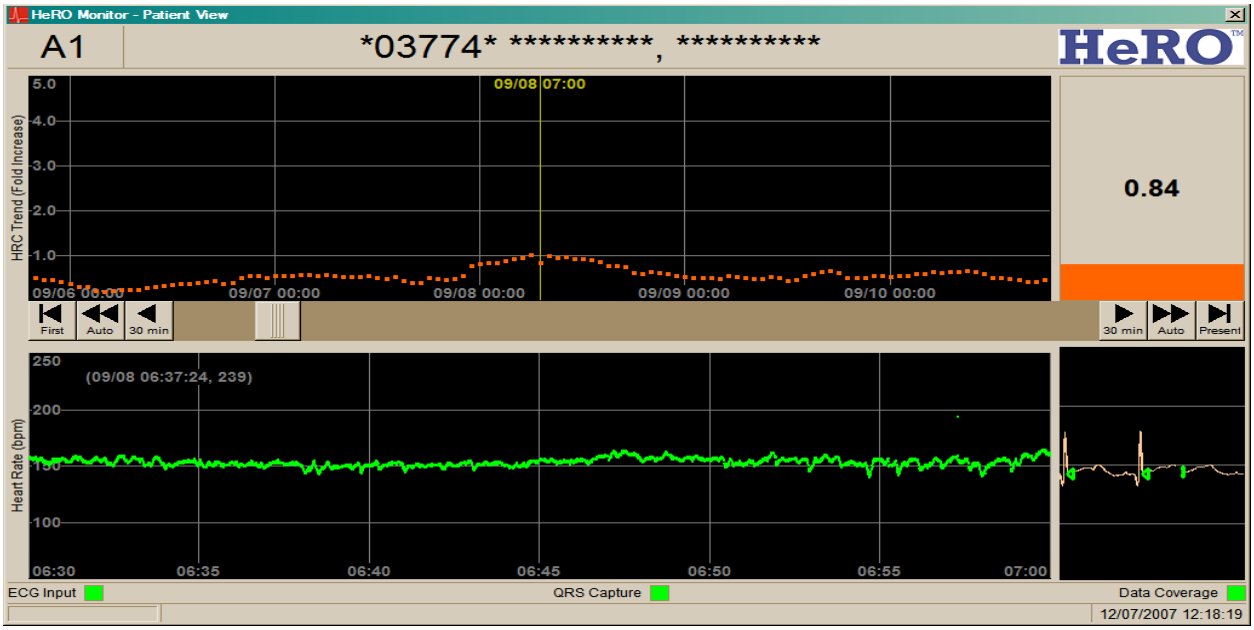


Figure C2

Patient presents as a Caucasian female, 770 grams at birth, 24 weeks gestational age. **HeRO Scores** were generated for this patient, but not displayed to clinicians. Clinical annotations are marked in blue. During the initial days in the NICU, the **HeRO Score** trends low. During the course of this example trend, the clinician is instructed to take no action based on the **HeRO Score**, although treatment should not be withheld if clinical signs of sepsis are present.

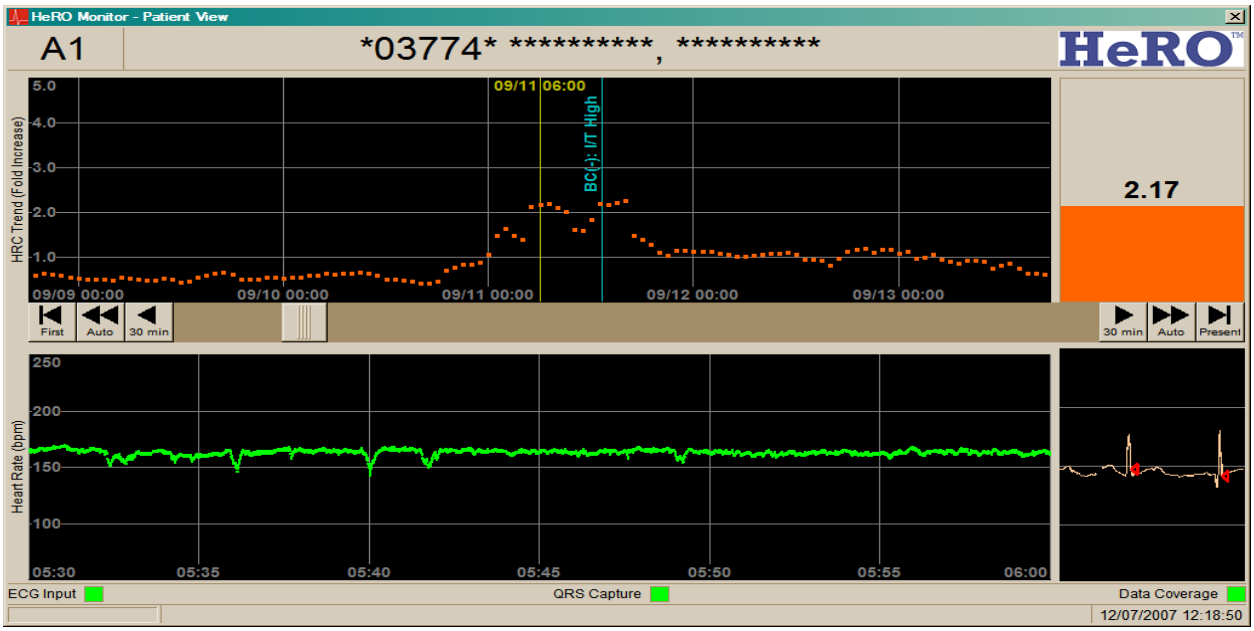


Figure C3

At approximately twelve days of age, the patient exhibits episodes of reduced heart rate variability punctuated by transient decelerations. This causes the **HeRO Score** to rise approximately 12 to 18 hours prior to an episode of clinical sepsis (i.e. sepsis observed clinically and treated with antibiotics without confirmation by blood culture). In this example, if the **HeRO Score** were present, the clinician is instructed to obtain the lab work when the **HeRO Score** first went above 2.0, eight hours prior to the culture time.

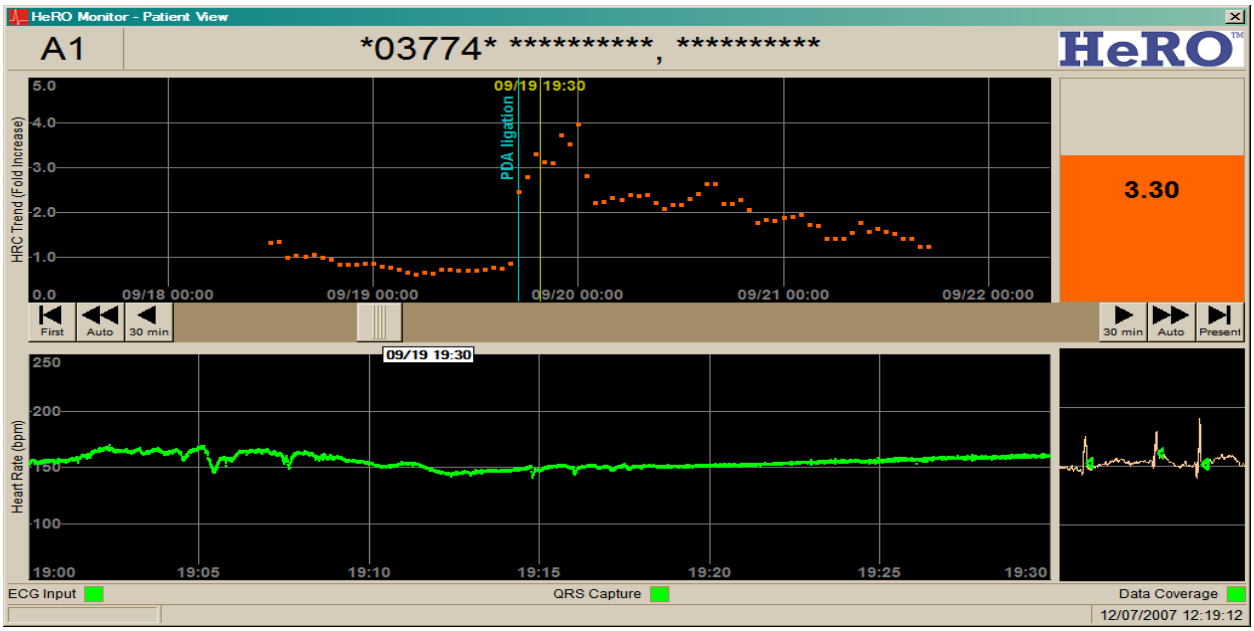


Figure C4

At approximately three weeks of age, the patient returns from surgery. Anesthesia results in a complete loss of variability in the heart rate, and a corresponding elevation in the **HeRO Score**. Over the next 48 hours, variability returns to the heart rate and the **HeRO Score** returns to normal. In this example, the clinician is instructed to ignore the elevated **HeRO Score** because it was caused by anesthesia.

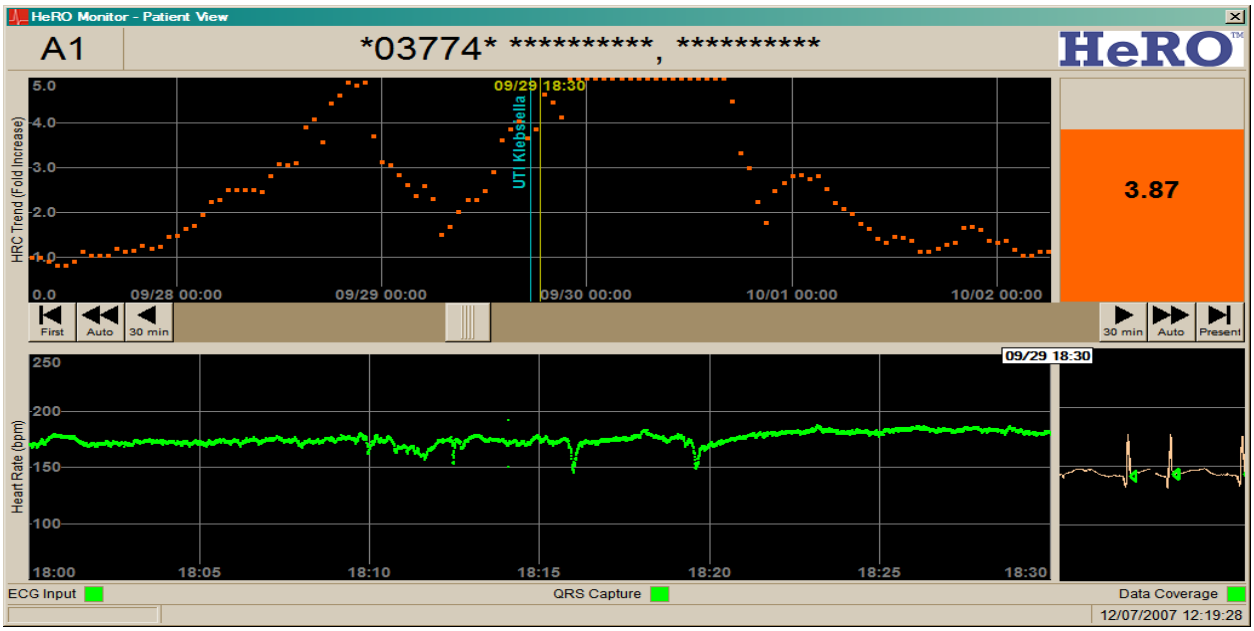


Figure C5

At approximately four weeks of age, the patient again exhibits a loss of variability punctuated by transient decelerations, resulting in a spike in the **HeRO Score** that begins approximately 36 hours prior to the diagnosis of Urinary Tract Infection with Klebsiella (the blue line indicates the time the culture sample was taken). In this example, the clinician is instructed to begin lab work at the first elevation of the **HeRO Score** above 2.0, approximately 36 hours prior to the urine culture.

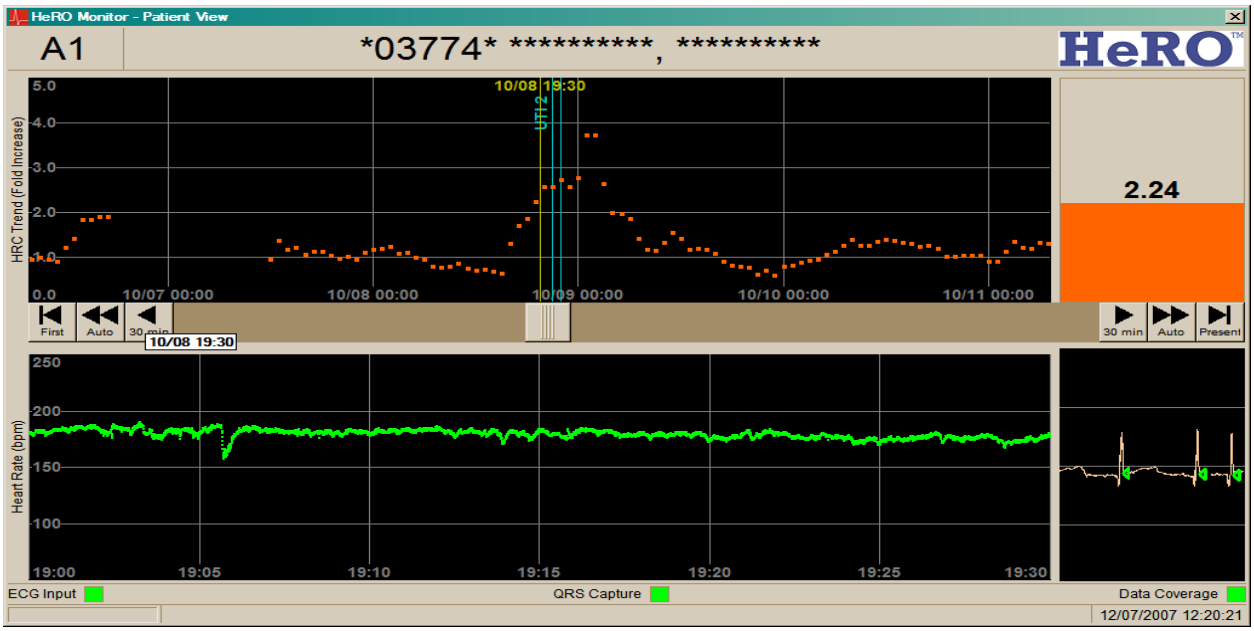


Figure C6

At approximately six weeks of age, the patient's **HeRO Score** again spikes, in this case 3 to 5 hours prior to diagnosis of another UTI. In this example, the clinician is instructed to begin lab work at the first elevation of the **HeRO Score** above 2.0, approximately two hours prior to the urine culture.

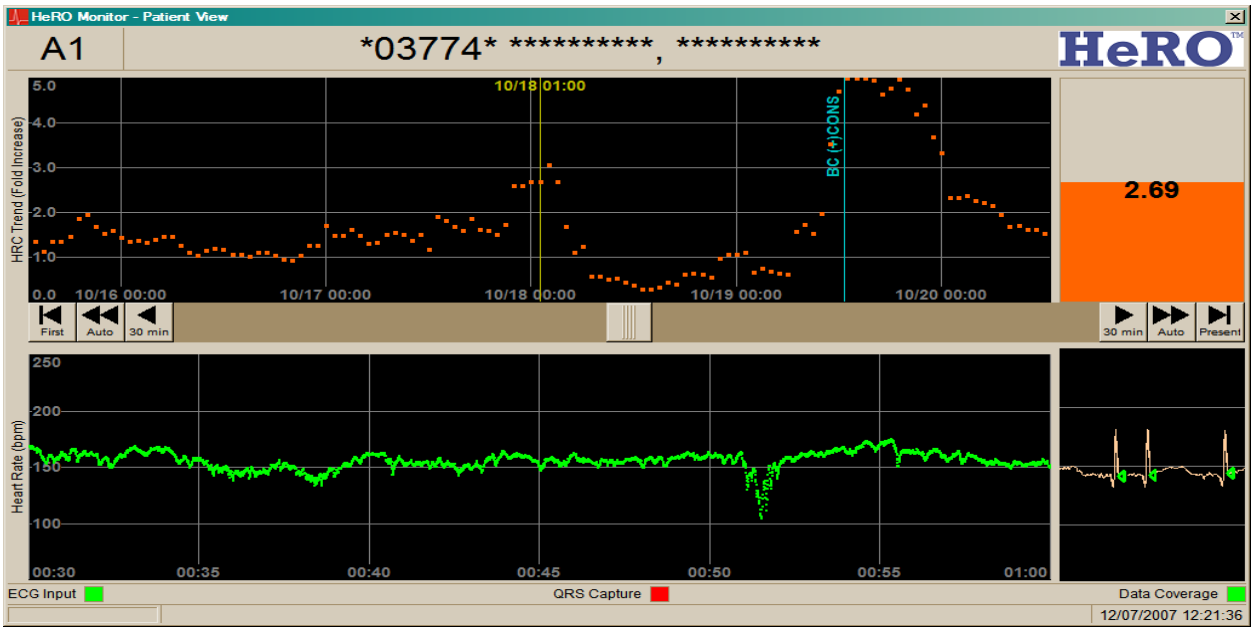


Figure C7

At approximately seven weeks of age, the patient's **HeRO Score** again spikes prior to diagnosis. In this case, the blood culture was positive for coagulase negative staphylococcus. In this example, the clinician is instructed to begin lab work at the first elevation of **HeRO Score** above 2.0, approximately 36 hours prior to the blood culture.

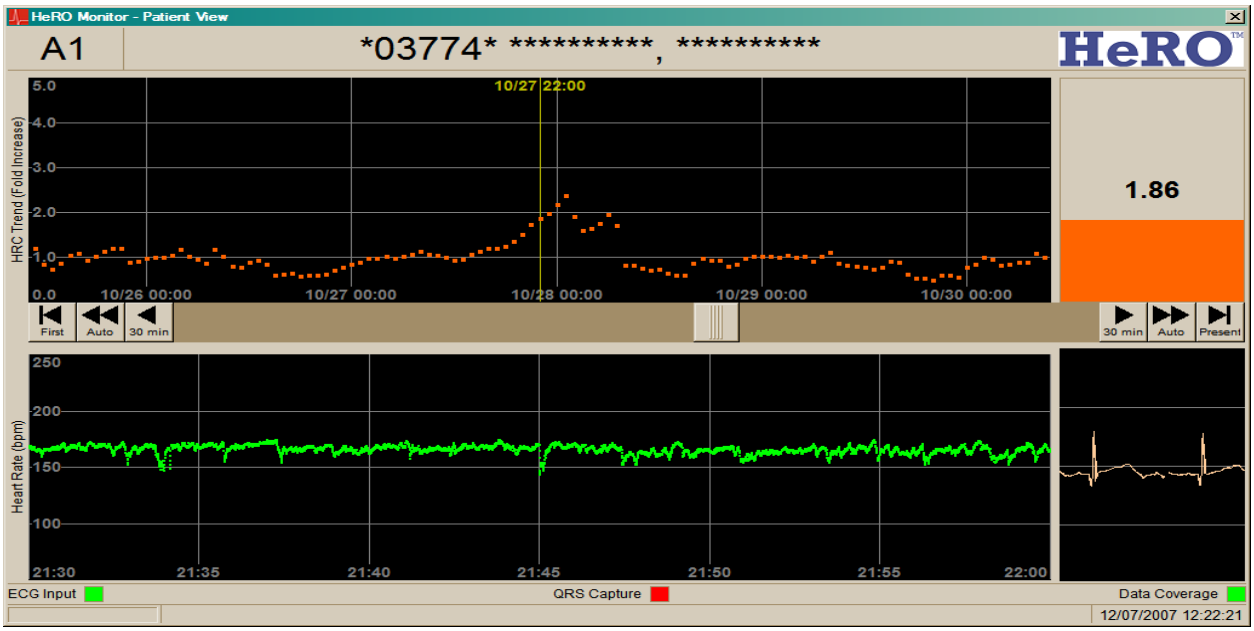


Figure C8

At approximately eight weeks of age, the patient exhibits a spike in **HeRO Score** that is not associated with any clinical event (i.e. a False Positive). In this example, the clinician is instructed to begin lab work at the first elevation of the **HeRO Score** above 2.0, which would have led to an unnecessary heel stick (presumably).

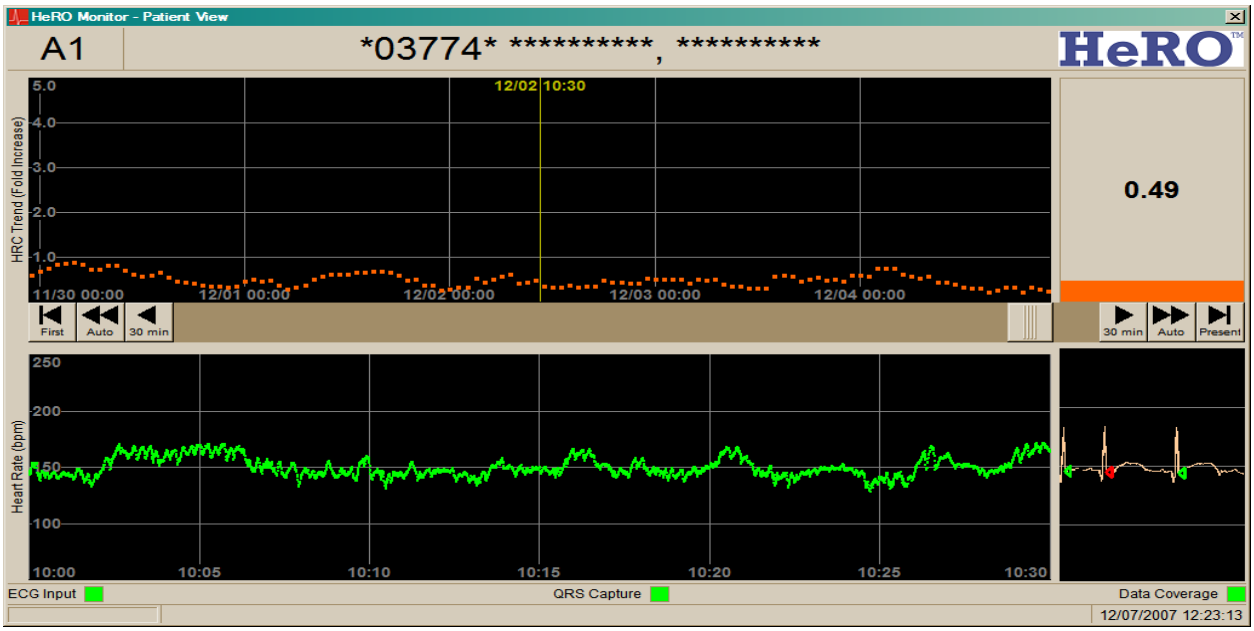


Figure C9

The remainder of the patient's stay in the NICU is marked by a low trend of **HeRO Scores**. The patient is discharged home after 94 days in the NICU. In this example, the clinician is instructed to take no action based on the **HeRO Score**.